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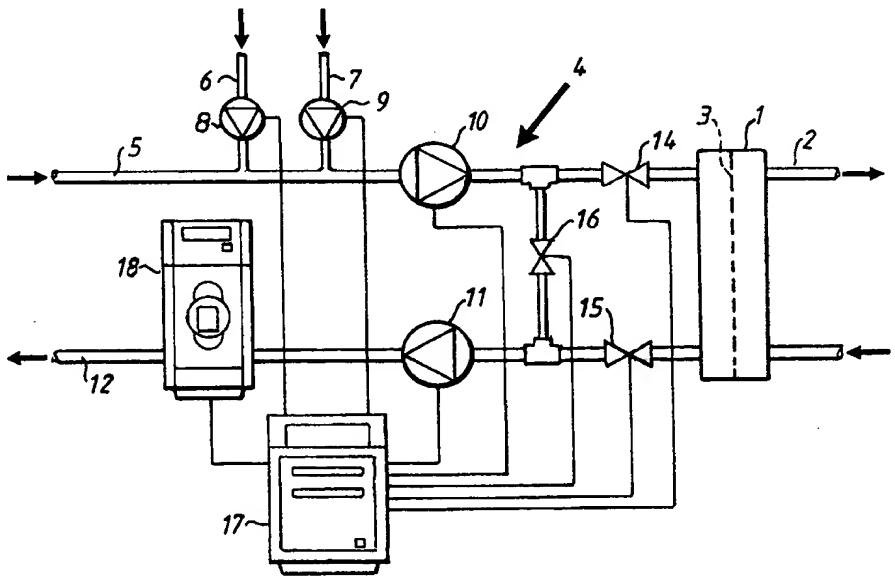

(57) Abstract

A method and apparatus for calculating the mass of a composition in a fluid volume or efficiency of exchange of said composition with an exchange fluid, especially urea in the body of a dialysis patient. Calculations are based on total mass of urea in the body. The concentration c_d of urea in the effluent dialysate is measured, and the total removed mass U of urea is calculated by integrating the product of the urea concentration c_d and the dialysate flow Q_d. The momentary relative efficiency of the removal (K/V) is determined essentially by calculating the slope of the logarithm of the concentration curve and the momentary mass is determined therefrom. Then, the pre-treatment mass of urea in the body can be determined very accurately. Moreover, the momentary relative efficiency in any point is determined by using the removed urea U. The dialysis dose is calculated by integrating the momentary efficiencies.

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TITLE

METHOD AND DEVICE FOR CALCULATING DIALYSIS EFFICIENCY

FIELD OF THE INVENTION

The present invention relates to a method and device for calculating dialysis efficiency using values obtained from a urea sensor for the calculations. The calculations can also predict certain conditions needing intervention.

BACKGROUND ART

In hemodialysis it is today common to dialyse a patient three times per week during a time period of three to four hours per treatment. The object of the treatment is to give an adequate dose of dialysis to the patient. Such a dose of treatment can be defined in different ways.

One commonly used definition uses the urea molecule as a marker molecule and prescribes that the dialysis clearance (K) divided by the distribution volume (V) of urea times total treatment time (t) should exceed a certain constant, for example Kt/V is greater than one per treatment. The weekly dialysis dose is then Kt/V greater than three.

One common way of measuring Kt/V is by measuring the concentration of urea (c_b) in the plasma before and after the treatment. The ratio $R = c_{bpost} / c_{bpre}$ is correlated to Kt/V. A number of different equations have been suggested for the calculation of Kt/V, such as:

$$Kt/V = -\ln(R - 0{,}03) \div (4 - 3{,}5 \cdot R) \cdot UF/W \qquad (1)$$

where UF = ultrafiltration volume removed in litres and W = postdialysis weight in kg.

Several clinical studies have been performed evaluating Kt/V in which postdialysis plasma urea c_{bpost} has been measured immediately after the dialysis, usually less than two minutes after ending the treatment. However, most patients have a rebound of c_{bpost}. If an equilibrated post treatment c_{bpost} is measured after for example 30 minutes, a more "true" Kt/V can be measured.

The measurement of c_b is not unproblematic. It is required that a blood sample is taken before and after the dialysis treatment. Such samples are then analysed by the hospital's laboratory. The resulting values are given with a substantial time delay. In this way it is not possible to adjust the actual treatment so that a prescribed dose is obtained.

The post treatment sample must be taken with care, especially regarding timing, to avoid false values due to cardiopulmonary or access recirculation. Another source of error is rebound mentioned above.

If an equilibrated post treatment sample should be taken, such sample should be taken 30 - 60 minutes after terminating the treatment which is not practical for the patient. The amount of rebound and the rate of rebound varies considerably from patient to patient.

These problems have been addressed in the prior art in different manners.

WO 94/08641 describes the use of a urea monitor for assessing the adequacy of an dialysis treatment. The urea monitor is connected to the dialysis effluent line and measures the concentration of urea in the dialysate leaving the dialyzer.

According to this specification, it is necessary to know or measure the predialysis plasma urea value (c_{bpre}). Such measurements can be made by measuring the urea concentration in an equilibrated sample taken before the initiation of the

treatment. However, such initial measurement takes time and the dialysis machine needs to be specially constructed to obtain such predialysis urea value.

Other indicators of adequate dialysis are URR and SRI:

$$URR = 1 - R = 1 - c_{b\ post}/c_{b\ pre} \quad (2)$$

$$SRI = (m_{urea\ pre} - m_{urea\ post}) / m_{urea\ pre} \quad (3)$$

where $m_{urea\ pre}$ and $m_{urea\ post}$ are pre and post amounts of urea in the body, respectively.

SUMMARY OF THE INVENTION

The object of the present invention is to provide a method and a device for determining the efficiency of a dialysis treatment and monitoring delivered dose of treatment on-line.

Another object of the invention is to provide a method and device for continuously monitoring the dialysis efficiency for adjusting the dialysis treatment on line when required, for example if the dialyzer is clotted.

A further object of the invention is to provide a method and device for estimating the dose of dialysis delivered without the need for taking blood samples or requiring the dialysis machine to make any special adjustments such as taking an equilibrated predialysis plasma urea concentration.

According to the present invention, a urea monitor is used for measuring the urea concentration c_d in the effluent dialysate from a dialyzer and determine the total removed urea (U) during the treatment. The measured values are used by a calculation computer for estimating a predialysis urea mass m_0 and the relative efficiency K/V. Using these values, an indication of the dose of dialysis can be obtained on-line, for example by integrating the calculated K/V over the treatment time. Since the predialysis and postdialysis urea masses are calculated, SRI can be determined. URR can be determined as well if the distribution volume is estimated, for example with Watson's formula, see equations (2) and (3) above. Also equation

(1) could be used since R is known. It is noted that SRI and URR are obtained as equilibrated values.

According to another approach of the invention, it is assumed that the relative efficiency K/V is comparatively stable over at least smaller time periods and decreases continuously. If a sudden change in efficiency is determined, it could be an indication of an error condition possibly requiring nurse intervention, such as clotting of the dialyzer, or a change of blood flow Q_b.

According to still another approach of the invention, the effective clearance of the dialyzer is determined by introducing a disturbance into the dialyser and analyzing the effluent dialysate from the dialyser in view of the disturbance. The disturbance can be an alteration of the conductivity of the dialysis fluid. By the analysis of the results, it is possible to determine the effective clearance of the dialyser. By combining the dialysate concentration of urea and the effective clearance of the dialyser, the blood concentration of urea can be determined without any invasional method. By combination with the amount of urea obtained by the present invention, the distribution volume of urea can be estimated.

The measured concentration values of urea in the effluent dialysate solution has a scattered appearance for many reasons. However, by using a special curve adaptation algorithm, it is possible to evaluate the relative efficiency K/V over periods where it is relatively constant in order to accurately determine relevant dialysis parameters.

Further features appears from the patent claims annexed.

The invention and further objects, advantages and features thereof are described in more details below with reference to embodiments of the invention shown on the drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic view of a dialysis machine intended for hemodialysis including a urea monitor and where the invention can be used.

Fig. 2 is a schematic view similar to Fig. 1, but with the urea monitor integrated in the dialysis machine.

Fig. 3 is a schematic view similar to Fig. 1 of a dialysis machine adapted for hemofiltration.

Fig. 4 is a schematic view similar to Fig. 2 of a dialysis machine adapted for hemofiltration.

Fig. 5 is a diagram over concentration values obtained from the urea monitor in the dialysis machine according to anyone of Figs. 1 - 4.

Fig. 6 is an estimate of initial urea mass in the diagram according to Fig. 5.

Fig. 7 is a diagram similar to Fig. 5 but shows a dialysis treatment having a problematic portion.

Fig. 8 is an estimate of the initial urea mass in the diagram according to Fig. 7.

Fig. 9 is a schematic view similar to Fig. 2 and including means for inducing a disturbance in the dialyser.

Fig. 10 is a diagram similar to Fig. 5 for determining the blood concentration of urea.

DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is intended to be used for estimating parameters for a dialysis treatment, such as hemodialysis, hemodiafiltration or hemofiltration. It can also be used for some types of peritoneal dialysis. However, the invention is not limited to the above-mentioned treatment modes, but can be used also for non-medical purposes.

Fig. 1 is a schematic diagram of a dialysis machine where the present invention can be practised. The dialysis machine provides means for replacing the renal function of a mammal if the renal function is impaired or completely absent.

The blood from a patient is taken out into an extracorporeal circuit 2 including a filter or dialyzer 1, including a semipermeable membrane 3. The blood passes on one side of the membrane. At the other side of the membrane, a dialysis fluid is circulated by the dialysis machine 4.

The dialysis fluid is usually prepared by the machine from one or several concentrates and water to form a dialysis fluid having the desired properties. Thus, the machine disclosed in Fig. 1 comprises a water inlet 5, two concentrate inlets 6 and 7, and two concentrate metering pumps 8 and 9. A first main pump 10 propels the ready made dialysis fluid to the dialysis side of the dialyzer into contact with the membrane.

A second main pump 11 passes the effluent fluid from the dialyzer, the inlet dialysis fluid and any ultrafiltrate removed from the blood via the filter, further on to an outlet 12 and to the drain.

A by-pass line 13 is arranged between the first 10 and the second pump 11. Several valves 14,15,16 are arranged for controlling the flow of dialysis fluid. The valves and the pumps are controlled by a computer 17 as schematically shown by several lines in Fig. 1. Of course, the dialysis machine is provided with several other means as is conventional. These

other means are not disclosed, since they are not relevant for the operation of the present invention.

The first main pump 10 is driven with a speed so that the dialysis fluid delivered to the dialyzer is substantially constant, e.g. 500 ml/min. The second main pump 11 is driven with a slightly higher speed so that the effluent fluid, called the dialysate, has a flow rate of e.g. 515 ml/min. This operation generates a pressure at the dialysate side of the dialyzer, which is suitable for removing 15 ml/min of ultrafiltrate fluid from the blood, i.e. plasma water. During a treatment of 4 hours, such ultrafiltration means a fluid removal from the patient of 3,6 litres. Of course, the dialysis machine is operated so that the treatment prescribed to the patient is fulfilled.

In the effluent line from the dialysis machine is placed a urea monitor 18, which measures the urea concentration c_d in the effluent dialysate. The monitor can be positioned inside the dialysis machine or completely outside the dialysis machine. The urea monitor can be of the type disclosed in WO 96/04401. It is noted that this urea monitor has a conductivity sensor, so the conductivity of the dialysate is determined by the urea monitor and the urea concentration is calculated usin such conductivity measurements.

The urea monitor is shown connected to the computer 17 of the dialysis machine. However, the monitor can have a computer of its own.

The urea sensor or the dialysis machine also includes means for measuring the flow rate of the effluent dialysate, Q_d. The computer 17 is arranged to provide concentration values c_d as well as values of the total mass urea U removed during the treatment as the integral of $Q_d \cdot c_d$. The concentration values are taken continuously so that a concentration curve c_d can be obtained from the urea sensor as well as a mass curve U.

Fig. 2 discloses a similar dialysis machine as Fig. 1. The main difference is that the urea monitor 19 is placed between the dialyzer 1 and the second main pump 11 and before the outlet of the bypass line.

Fig. 3 discloses a similar dialysis machine as Fig. 1, but adapted for hemofiltration or hemodiafiltration. The only difference is that there is included an infusion line 20 including an infusion pump 21. The infusion line 20 starts from the outlet of the first main pump 10 and ends at the blood inlet side of the dialyzer, for providing an infusion fluid to the blood before the dialyzer, called preinfusion. The urea monitor 22 is arranged in the effluent dialysate line after the second pump 11.

Finally, Fig. 4 discloses a similar dialysis machine as Fig. 2, but adapted for hemofiltration or hemodiafiltration and providing an infusion fluid to the blood after the dialyzer, called postinfusion. The urea monitor 23 is placed before the second main pump 11 and before the outlet of the bypass line.

Fig. 5 discloses a typical urea concentration curve c_d obtained from the urea sensor. As appears from the figure, the curve is very irregular and includes several dips. These dips are obtained when the dialysis machine is connected for selfcalibration, when valve 16 is opened and valves 14 and 15 are closed.

Fig. 6 is a plot of urea mass values calculated according to the method disclosed in further details below.

Fig. 7 is a concentration curve obtained during a treatment having some problematic portions as also described closer below.

Finally, Fig. 8 is a plot of urea mass values calculated according to the method disclosed below.

There are several approaches to urea kinetics. One common approach is based on the assumption that urea is distributed in a single body compartment, the single pool model.

It is well known that the measured urea concentration during treatments does not follow such a model, specially at high efficiency treatments.

Another approach assumes that the urea is distributed in two distinct series connected body pools with a diffusive exchange of urea there between. This model can explain the noted rebound after treatment, and the more rapid removal of urea at the beginning of the treatment.

Still another approach assumes that the body is divided in several compartments communicating with the blood with different time delays.

In the present invention, a urea monitor is used to measure urea concentration in the effluent dialysate from a dialyzer. Moreover, the total amount of effluent dialysate is measured. Thus, it is possible to determine the urea concentration c_d times the total dialysate flow Q_d. By integrating the product of $c_d \cdot Q_d$, the total removed urea U is obtained.

If it is assumed that there is no accumulation of urea in the body, the total amount of removed urea (U) must be equal to urea generated (G) in the body over a certain time period, for example averaged over one week. This can be used for calculating the nutrition status or protein catabolic rate (PCR).

According to the present invention, the urea concentration measured by a urea monitor in the effluent dialysate solution from the dialyzer, is used for determining parameters of the dialysis as it progresses. These parameters are used for assessing the dialysis treatment on-line to determine the efficiency, the delivered dose, pre and post total urea masses in the body, urea generation rate, volume of distribution of urea in the body (for example by taking a blood sample for determining the urea concentration in the blood), and

still further parameters and variables as will become evident of the description to follow.

These estimations according to the present invention are independent of any assumptions about the distribution of urea in the body.

Thus, the present invention starts from the fact that no assumption should be made about the urea distribution in the body. Instead, the total amount of urea (m) in the body at each moment is considered. According to the invention, the definition of mean urea concentration is the mean concentration of urea in the body over a distribution volume (V).

Neither the distribution volume, nor the mean urea concentration can be measured but we can use them for calculations. They can, however, be measured indirectly through the urea concentration measured in the effluent dialysate by the urea monitor as explained below.

Moreover, according to the invention, the normally used dialyzer clearance is replaced by a whole body clearance K defined as the ratio between urea mass removal rate and mean urea concentration c_m in the body. The urea mass removal rate is measured by the urea monitor and is the urea concentration (c_d) in the effluent dialysate times the effluent dialysate flow (Q_d). Consequently, these definitions are:

$$K = Q_d \cdot c_d / c_m \quad (4)$$

$$m = c_m \cdot V \quad (5)$$

Since the rate of change of the urea mass in the body is urea generation rate (G) minus urea mass removal rate $Q_d \cdot c_d$ the following equation is valid:

$$dm/dt = G - Q_d \cdot c_d = G - m \cdot K/V \quad (6)$$

This is a first order differential equation with time-varying coefficients which can be solved by standard methods. If we presume that K and G are constant and that V is a linear function of t ($V = V_0 - UF \cdot t$), we find that:

$$\int_0^T \frac{K}{V} ds = \ln\left[\frac{m_0 - \frac{G \cdot V_0}{K-UF}}{m_T - \frac{G \cdot V_T}{K-UF}}\right] = -\ln\left[1 - \frac{m_0 - m_T - \frac{G \cdot T \cdot UF}{K-UF}}{m_0 - \frac{G \cdot V_0}{K-UF}}\right] =$$

$$= -\ln\left[1 - \frac{U - G \cdot T \cdot \frac{KT/V_0}{KT/V_0 - \Delta W/V_0}}{m_0 - \frac{G \cdot T}{KT/V_0 - \Delta W/V_0}}\right] \qquad (7)$$

The assumption made for arriving at equation (7) is that the whole body clearance K is constant throughout the treatment.

Alternatively, it can be assumed that the relative efficiency K/V is constant, which results in a similar equation:

$$\int_0^T \frac{K}{V} ds = \ln\left[\frac{m_0 - \frac{G \cdot V_0}{K}}{m_T - \frac{G \cdot V_T}{K}}\right] \qquad (8)$$

However, we have found that K and K/V, respectively, are not constant throughout the complete treatment, but are usually larger during an initial period of the treatment during the first 30 - 60 minutes and then approximately constant.

Moreover, equations (7) and (8) require the initial amount of urea, m_0, which must be measured prior to the dialysis treatment, for example by a blood sample or by equilibrated dialysate as described in WO 94/08641 and by estimating the distribution volume of urea in the body.

However, the need for taking an equilibrated blood sample 30 - 60 minutes after the treatment has been eliminated since the equation calculates the accumulated Kt/V continuously so that the treatment can be terminated when the desired dose has been achieved.

Another object of the present invention is to take a further step in using the data obtained from the urea monitor to obtain all data needed for estimating important parameters of the complete treatment. By using the idea of whole body urea mass and whole body clearance K, it is possible to develop equations which are independent of any assumption about constant clearance K or constant relative efficiency K/V over the complete treatment period.

By combining equations (4) and (5), and by integrating the left portion of equation (6) we obtain:

$$m = (Q_d \cdot c_d) / (K/V) \quad (9)$$

and

$$m = m_o + G \cdot t - U \quad (10)$$

where

G = urea generation which is assumed constant

U = total removed urea, which is equal to the integral of $Q_d \cdot c_d$ obtained from the urea monitor.

By rearranging we obtain:

$$K/V = (Q_d \cdot c_d) / (m_o + G \cdot t - U) \quad (11)$$

or

$$m_o + G \cdot t = U + (Q_d \cdot c_d) / (K/V) \quad (12)$$

Equations (11) and (12) are independent of any assumptions of the urea distribution in the body or any assumption of constant K. The only assumption made is that G is constant. However, if G is not constant, the product $G \cdot t$ should be replaced by the integral of G over t.

Equation (11) can be used to evaluate the time dependence of K/V, which can be used for some purpose to be explained in more details below.

Like in equations (7) and (8), it is necessary to obtain the initial amount of urea m_0 in the distribution volume V of the body for equations (11) and (12).

It is possible to obtain that value by taking a blood sample before the initiation of the dialysis and by estimating the distribution volume, for example by using Watson's formula.

Another method is to allow the dialysate to equilibrate with the blood at the initiation of the dialysis treatment and measure the dialysate concentration, whereby the dialysate concentration equals the blood water concentration. By estimating the distribution volume, for example by Watson's formula, the initial mass of urea m_0 can be obtained.

By these methods, it is possible to obtain a value of the initial mass m_0 of urea, which can be used in equation (11) for obtaining the momentary relative efficiency K/V. By integrating K/V over time, an estimate of the delivered dose Kt/V is obtained.

On the average, Watson's formula gives a good estimate of the distribution volume for a population of patients. However, the error for a specific patient may be large and difficult to predict. This may result in a large error in the estimate of initial mass m_0.

On the other hand and according to the present invention, it has been found that the initial mass m_0 can be calculated by using only the data obtained from a urea monitor, which measures the urea concentration c_d in the effluent dialysate from a dialyzer and the flow of dialysate Q_d.

We can see that the left portion of equation (12) is a straight line with the slope G. The variables c_d and Q_d as well as U ($dU/dt=Q_d \cdot c_d$) are measured by the urea monitor. If we know K/V in at least two points, it is possible to calculate the constants m_0 and G.

It is also possible to determine G from the total removed urea during one week, which should be equal to the

generation if steady state is presumed, i.e. the generation equals the removal. If the patient is dialysed three times per week, the removed urea during one such dialysis treatment can be used for estimating the generation, as disclosed by Garred et al.

If the constant m_0 is calculated from several measured values, it is possible to obtain a more accurate value of m_0 by taking the mean value or median value or other statistical value from all calculated values of the constant m_0.

In order to continue further, it is necessary to make an assumption about the time dependence of K/V.

Firstly, it is assumed that the instantaneous relative efficiency K/V is constant over at least some time period during the treatment. The dialysis curves obtained seem to validate that there should be at least some periods with constant K/V, at least in dialysis with low ultrafiltration UF. It can be assumed that V is a linear function of time with constant ultrafiltration. However, it seems that the clearance K also varies with time in a similar manner, at least over certain time periods.

Taking the derivative of equation (12) with constant K/V we obtain:

$$G = dU/dt + Q_d \cdot (V/K) \cdot dc_d/dt \qquad (13)$$

By inserting $dU/dt=Q_d \cdot c_d$ we obtain:

$$\frac{dc_d}{dt} + \frac{K}{V} c_d = \frac{G}{Q_d} \bullet \frac{K}{V} \qquad (14)$$

By integrating and taking the logarithm of equation (14) we obtain:

$$\ln(c_d - G/Q_d) = \ln(c_0 - G/Q_d) - Kt/V \qquad (15)$$

The curve of equation (15) is a straight line with the slope K/V. As appears from equation (15), the dialysate concentration value c_d has to be reduced by an offset term G/Q_d related to the generation.

Thus, by using equation (15) in a period where the slope of the curve is constant, the momentary relative efficiency K/V can be determined in a number of points. Thence, by using equation (12), m_0 can be calculated for each point and an averaged (mean or median) value of m_0 can be estimated.

Secondly, it is assumed that K is constant over at least some time period during the treatment. The dialysis curves obtained seem to validate that there should be at least some periods with constant K. We also presume that during said time period the distribution volume of urea in the body V is a linear function of time t with a constant ultrafiltration UF:

$$V = V_0 - UF \cdot t \qquad (16)$$

By taking the derivative of equation (12) we obtain:

$$G = dU/dt + (Q_d \cdot V/K) \cdot dc_d/dt - (Qd \cdot c_d/K) \cdot dV/dt \qquad (17)$$

which results in:

$$dc_d/dt + c_d \cdot (K - UF)/V = (K/V) \cdot G/Q_d \qquad (18)$$

Equation (18) can be solved:

$$C_d(t) - \frac{G}{Q_d(1-UF/K)} = \left\{C_d(0) - \frac{G}{Q_d(1-UF/K)}\right\} \bullet \left(\frac{V}{V_0}\right)^{\frac{K-UF}{UF}} \qquad (19)$$

The expression $G/[Q_d\ (1\ -UF/K)] = c_k$ is an offset term for the measured dialysate concentration c_d due to urea generation G. The dialysis concentration c_d will approach this offset c_k asymptotically for long treatment times.

Thus:

$$\ln(c_d-c_k) = \ln(c_0-c_k)+ [(K-UF)/V_0]\cdot[(V_0/UF)\ln(V/V_0)] \quad (20)$$

where

$$[(V_0/UF)\ln(V/V_0)] = (V_0/UF)\ln(1-t\cdot UF/V_0) \cong -t \quad (21)$$

By plotting the left member of equation (20) versus $[(V_0/UF)\ln(V/V_0)]$ it is possible to determine the slope $[(K-UF)/V_0]$. The ultrafiltration UF is constant and known. Thus, the relative efficiency K/V_0 can be determined, if UF/V_0 is estimated. By using equation (12), m_0 can be determined, if the urea generation (G) is known. Otherwise, the urea generation can be determined as the time varying component of the determined m_0.

The determination of m_0 is made only over the time period where it is found that K or K/V, respectively, are constant, i.e. where the measured data fit equations (15) or (20) well enough.

As can be seen from the enclosed diagram, Fig 3, over a dialysate concentration curve from a typical patient, c_d is very irregular due to inter alia bypass periods, cell-to-cell checks in the urea monitor, noise and changes in the treatment efficiency (K/V) for various reasons.

It is not easy to find a curve which is the best fit for a certain time period where K or K/V should be constant. However, the Hough transform (US 3069654), used for finding lines in images, is a method capable of handling such types of disturbances. The Hough transform looks for straight lines that passes through the largest number of points. So even if a large number of points are outside the line, this method can still

work. It will also find several lines, if there are changes in the treatment efficiency.

According to the preferred embodiment of the present invention, the following steps are performed.

The urea generation rate G is estimated from patient data, for example removed amount of urea during a week.

A continuous measurement is performed in the effluent dialysate of urea concentration c_d. At the same time the urea concentration c_d times the dialysate flow rate Q_d is integrated to provide the total removed urea U.

The measurement is started at time zero, which is defined as the time where the measurement of urea concentration exceeds a certain level during more than five minutes.

From time zero, the urea concentration c_d is plotted versus time and the total removed urea U is calculated by integrating the urea concentration c_d times Q_d.

Then, there is a waiting period of for example 60 minutes, where it is assumed that K or K/V may be changing.

After the waiting period, the data of the urea concentration curve is processed by subtracting the offset term G/Q_d from the urea concentration c_d and plotting the logarithm of the corrected urea concentration. Then, the curve is processed for finding a portion where K/V is substantially constant, as discussed above in connection with equation (15). This is performed by using the Hough transform of finding a line which passes through the largest number of points on the logarithm of the corrected urea concentration curve. When a portion of sufficient length has been located, the slope of the curve is determined for calculating K/V.

Then, a number of measurement values of the urea concentration c_d is selected which are within a certain deviation from the line obtained by the Hough transform, for example within 1% from the line. For these points, the instantaneous mass of urea is calculated by using equation (9..

Finally, these instantaneous mass values are referenced to time zero, as defined above, by using equation (10) for obtaining several calculated values of m_0. The median value of these calculated initial mass values are regarded as the best estimate of the initial mass m_0 of the body.

Our research has shown that the estimate of the initial urea mass is very accurate. Thus, the estimate of the efficiency and dose of the treatment based on this invention are also very accurate.

When the initial urea mass m_0 has been obtained, it can be used in many different ways to estimate the efficiency of the treatment.

The dose of the treatment can be calculated by using equation (11) to obtain K/V at each moment of time. Then, K/V is integrated over the time to obtain Kt/V. When the desired dose has been obtained, the dialysis treatment is terminated.

If the distribution volume V_0 of urea in the body is estimated, the initial urea blood concentration $c_{b\ pre}$ in the body can be obtained without the need for taking any blood sample by dividing the estimated mass m_0 with the distribution volume V_0. Since the total removed urea U is calculated continuously, the urea mass after the dialysis treatment is known and the post urea blood concentration $c_{b\ post}$ can be estimated since ultrafiltration is also known. The post urea concentration is the equilibrated urea concentration, since the method according to the present invention calculates on total urea mass in the body.

Thus, URR or SRI can be calculated according to equations (2) or (3). Moreover, equation (1) can be used for estimating the dialysis dose Kt/V.

The obtained determination of the initial mass m_0 can be used for calculating the urea distribution volume V of the patient, for example after completion of the dialysis session. First, the initial urea concentration in blood $c_{b\ pre}$ is measured

before the dialysis to obtain a value of the mean urea concentration before dialysis, for example by a blood sample or equilibrated dialysate measurement. This urea concentration is equal to the "mean" urea concentration according to the present invention, since urea is initially equally distributed in the body of a patient. Then, the distribution volume V_{pre} (V_0) can be calculated by dividing the initial urea mass m_0 as calculated according to the present invention with measured blood concentration $c_{b\ pre}$. Finally, the ultrafiltration volume removed during the treatment is subtracted to obtain V_{post}, i.e. the distribution volume of urea after the dialysis treatment. This post distribution volume V_{post} should be fairly constant for a normal patient in a steady state and can be used as an additional clinical parameter.

There are many alternative methods of using the principles of this invention. For example, it is possible to use the alternative method where K is assumed constant as discussed in relation to equations (16) to (19).

Instead of using the urea concentration values which are within 1% from the Hough transform line, the line itself can be used for the calculations. Moreover, the total removed urea U curve can be approximated with one or several exponential curves using the Hough transform.

Other types of curve adaptation algorithms can be used. Thus, it is possible to use the least squares method. In that case, it is necessary to remove the data portions where the dialysis machine has made some self-calibration etc. This can be done in an iterative manner, where a first approximation is made and all data portions outside a certain limit, such as 10%, are removed and the process is repeated.

In certain types of dialysis machines, the dialysis treatment is interrupted regularly for self-calibration of the machine. In that mode, valve 16 is opened while valves 14 and 15 are closed, see Fig. 1. Thus, the dialysis of the blood ceases

after a short while when the dialysis solution inside the dialyzer has obtained equilibrium with the blood. In the urea concentration curves such self-calibration periods are visible by regular dips in the curve, see Fig. 5, where such self-calibration is carried out with 30 minutes intervals. After each such self-calibration, the dialysis starts again at a slightly higher level.

In order to account for such intermittent stops in the dialysis, the time scale should be adjusted to remove a portion of the stop period, since there is obviously no dialysis at least during a portion of the stop period. We have found that the best approximation to reality is obtained if the stop period is replaced by a period of 30 seconds. This is substantially independent of the actual length of the stop period, which can be anything from 35 seconds to several minutes.

As explained above, it is possible with the present invention to obtain a value of the initial mass of urea in the body of a patient. The invention can also be utilised in other areas, where it is of interest to know the mass of a substance or composition, such as in a beer brewery.

Other substances than urea can be monitored, such as creatinine, sodium, potassium, calcium, magnesium, bicarbonate, glucose, $ß_2$-microglobuline, etc. It is also possible to monitor the conductivity of the plasma water or blood or the osmolarity thereof. It is also possible to use the principles of the invention in connection with gases, such as oxygen gas, nitrogen gas or carbon dioxide gas.

If the invention is to be used for compositions in the body having some active mechanism interfering in the body, such as for sodium and potassium ions, such interaction should be taken account for.

For sodium and potassium and some other solutes, it is customary to include some concentration of these ions in the fresh dialysis solution and therefor it is necessary to

calculate on the difference between initial concentration and final concentration in the effluent dialysate from the dialyzer. One approach is to replace the concentration value c_d by the concentration difference c_{dout} minus c_{din} and the mean concentration c_m by the difference between the mean concentration and the initial dialysis fluid concentration, i.e. c_m minus c_{din}. Consequently, equation (4) at page 9 will essentially be replaced by:

$$K = Q_d \cdot (c_{dout} - c_{doin}) / (c_m - c_{din}) \qquad (22)$$

If the treatment has followed a standard treatment with no apparent complications, the dialysis dose can be calculated by using the initial and final dialysate urea concentrations c_{dpre} and c_{dpost} and using the equation:

$$URR = 1 - c_{d\ post}/c_{d\ pre} \qquad (23)$$

If the URR calculated using the method according to the present invention differs substantially from the URR obtained with equation (23), it is an indication of problems during the dialysis, such as clotting of the dialyzer, which otherwise could have passed undetected.

For determining the urea mass by equations (15) or (19) it is assumed that the concentration follows an exponential curve over at least a portion of the curve. Since the removed urea mass U is the integral of the concentration c_d multiplied by the dialysate flow Q_d (which is constant), it follows that also U is an exponential curve over at least a portion thereof. Consequently, it is possible to use U instead of c_d for calculating the momentary relative efficiency.

Alternatively, U can be used for verifying that the calculations using the concentration c_d are correct. Thus, it can be assumed that U approaches an asymptote which is:

$$Asy = m_0 + G \cdot t - G / (K/V) \qquad (24)$$

Since all these constants are obtained via the equations given above, it is easy to calculate U minus Asy to see if this curve is an exponential curve with the same exponent as the concentration curve. If this is not the case, there is probably some error.

According to the invention, the initial mass of urea is determined and several clinical parameters are calculated therefrom. However, the blood concentration of urea cannot be obtained, but needs to be measured by taking a blood sample and analysing it later, or by equilibrated ultrafiltration before the dialysis treatment is started. However, it is possible to determine the effective clearance of the dialyser with a method where a distrubance is introduced into the dialyser and the resultant effect on the effluent dialysate is analysed.

Such a method is shown in Fig. 9 which is a schematic view similar to Fig. 2. In the dialysis circuit is added a pump 24 connected to the inlet of the dialyser between the valve 14 and the dialyser 1. To the other side of the pump 24 is connected a bag 25 comprising a material to be added to the dialysis circuit via pump 24.

Moreover, Fig. 9 shows a pump 26 connected to the blood circuit at the inlet of the dialyser 1 for introducing a material comprised in a bag 27 connected to the other side of the pump 26.

Any of these devices can be used for introducing a disturbance to the inlet of the dialyser. It is also possible to produce a disturbance by operating the concentrate pumps 8 and/or 9.

The disturbance is a change of a parameter of the dialysis fluid or the blood. The disturbance can be a change of the conductivity or a change of the urea concentration. It is

noted that the urea monitor can measure both urea concentration and conductivity in the effluent dialysate. If another measurement instrument is used, any other substance can be used as a disturbance, as soon as it is compatible with the body, such as sodium, bicarbonate etc.

The influence by the dialyser on the disturbance is measured downstream of the dialyser, for example by the urea sensor. A portion of the disturbing material will pass the membrane from the dialysate to the blood or vice versa. The amount passing the membrane is dependent on the dialysance of the membrane.

If the disturbance is a step change in the conductivity, produced by pumps 8,9 the dialysance of the dialyser can be determined according to equation (see EP 547 025, the contence of which is included in the present application by reference):

$$D_e = Q_d \left[1 - (C_{dout2} - C_{dout1}) / (C_{din2} - C_{din1})\right] \qquad (25)$$

where

D_e = effective dialysance of the dialyser

Q_d = effluent dialysate flow

C_{dout1} and C_{dout2} = concentration in the effluent dialysate

C_{din1} and C_{din2} = concentration in the introduced dialysis fluid

Indexes 1 and 2 indicates before and after the step change. The introduced concentration can be measured or be determined by the set values of the concentration pumps.

It is also possible to determine the effective dialysance of the dialyser by the method disclosed in EP 658352 where three concentrations are measured and the dialysance is determined as disclosed in said patent specification, the contence thereof being included in the present application by reference.

An alternative method of determining the effective dialysance is disclosed in EP patent application No. 9715818,

the contence of which is included in the present application by reference. The dialysance is determined by the formula:

$$D_e = Q_d \times (1 - S_{out}/S_{in}) \quad (26)$$

where:

D_e = effective dialysance of the dialyzer

Q_d = dialysate flow emitted from the dialyzer

S_{out} = integral of Qd x (cd(t) - cd0) during the disturbance in the flow emitted from the dialyzer

S_{in} = integral of Qd x (cd(t) - cd0) during the disturbance in the flow entered into the dialyzer

The disturbance can be a change of conductivity or a change of urea concentration or any other substance that can be measured and is compatible with the body.

After obtaining the effective clearance of the dialyser with any of the above-mentioned method, it is observed that urea monitor measures the concentration of urea in the effluent fluid continuously. Thus, the urea concentration at the start of the treatment can be extrapolated from the first 5 to 20 minutes of treatment as shown in Fig. 10. Then, the plasma water concentration of urea in the body at the start of the treatment can be determined according to the formula:

$$c_{pw} = Q_d \times c_d / K_e \quad (27)$$

where

c_{pw}=plasma water concentration of urea at initiation of dialysis

Q_d = effluent dialysate flow rate

c_d = concentration of urea as extrapolated to the initiation

K_e = effective clearance of the dialyser for urea

Since the plamsa water concentration of urea can be calculated as indicated above and the amount of urea at the start of the treatment is estimated according to the present invention, the distribution volume V of urea in the body can be calculated. This distribution volume V is an important clinical parameter, which now can be measured with high accuracy.

The invention has been described in connection with removing a substance from the body, such as urea. The same principle is valid for the addition of a substance to the body, such as bicarbonate, acetate or lactate, etc.

The invention has been described in connection with a urea monitor, which measures the urea concentration in the dialysate continuously. It is also possible to use a measurement apparatus which measures the concentration intermittently, for example with one or a few minutes interval.

In principle, the invention can also be used for peritoneal dialysis, where the effluent dialysate is monitored for a certain substance or composition. Specially at tidal automatic peritoneal dialysis, where the dialysate in the patient is partially replaced periodically, the principles of this invention could be applied.

The invention has been described above with reference to the embodiments shown in the drawings. The various components and characteristics can however be combined in different ways than have been shown in the drawings and other combinations are included within the scope of the invention. The invention is only limited by the appended claims.

CLAIMS

1. A method for calculating the mass of a composition in a fluid volume, comprising:

performing mass exchange between said volume and an exchange fluid flow,

repeatedly measuring the concentration of said composition in the exchange fluid flow after said mass exchange for obtaining a concentration curve,

characterized by

fitting an approximation curve to at least a portion of said concentration curve, where the logarithm of said approximation curve is a substantially straight line,

determining a parameter of said approximation curve for use in calculating the mass of said composition in said volume.

2. A method as claimed in claim 1, **characterized** in that said composition in a fluid volume is a solute in a liquid volume.

3. A method as claimed in claim 2, **characterized** in that said mass exchange is performed by passing said solute and liquid on one side of a semipermeable membrane in a dialyzer and said exchange fluid is a dialysis liquid passing on the other side of said membrane resulting in a dialysate liquid exiting the dialyzer.

4. A method as claimed in claim 3, **characterized** in calculating the accumulated mass of said solute in said dialysate liquid by measuring the flow rate Q_d of said dialysate liquid flow and integrating the product of said flow rate Q_d and said solute concentration difference c_d over time.

5. A method as claimed in claim 3 or 4, **characterized** in that said dialysis liquid entering the dialyzer comprises a non-zero initial concentration of said composition, and that measuring of the concentration is replaced by measuring the concentration difference across the dialyzer.

6. A method as claimed in claim 3, 4 or 5, **characterized** in that said fitting of an approximation curve involves subtracting a compensation term (G/Q_d) from said solute concentration c_d to obtain a compensated concentration, taking the logarithm of said compensated concentration and fitting a straight line to said logarithm of said compensated concentration, where said compensation term compensates for generation (G) of said solute.

7. A method as claimed in any one of the preceding claims, **characterized** in that said parameter of said approximation curve is a slope of said substantially straight line.

8. A method as claimed in any one of the preceding claims, **characterized** in that said fitting is excluded for data obtained during an initiation period, of for example 60 minutes.

9. A method as claimed in any one of claims 3 to 8, **characterized** in that said flow of dialysis liquid is periodically interrupted for a first time period, and the time scale is adjusted by replacing said first time period with a replacement time period which is shorter than said first time period.

10. A method as claimed in any one of claims 3 to 9, **characterized** in that said parameter is the slope (K/V) with respect to time (t) of equation:

$$\ln(c_d - G/Q_d) = \ln(c_0 - G/Q_d) - Kt/V \quad (I)$$

where

c_d = dialysate concentration at time t

G = solute generation

Q_d = dialysate flow

c_0 = dialysate concentration at time zero

K/V = relative dialysis efficiency

t = time from time zero.

11. A method as claimed in any of the preceding claims, **characterized** in that a momentary mass (m_1) is determined according to the equation:

$$m_1 = (Q_d \cdot c_{d1}) / (K/V)_1 \quad (II)$$

where $(K/V)_1$ is determined for exampel according to equation (I), and in that the momentary relative efficiency $(K/V)_2$ at any time is determined according to equation:

$$(K/V)_2 = (Q_d \cdot c_{d2}) / m_2 \quad (III)$$

where

$$m_2 = m_1 - (U_2 - U_1) + G\,(t_2 - t_1) \quad (IV)$$

and

c_{d1} = concentration at time t_1

c_{d2} = concentration at time t_2

U_1 = accumulated mass to time t_1

U_2 = accumulated mass to time t_2.

12. A method as claimed in claim 11, **characterized** in that the momentary relative efficiency (K/V) is integrated over time to give an estimate of the total dialysis dose Kt/V.

13. A method as claimed in claim 11 or 12, **characterized** in that the fitting of said approximation curve is performed by calculating a line which passes through the greatest number of points in the logarithm of the concentration curve, possibly compensated.

14. A method as claimed in claim 13, **characterized** in that all values of concentration which are within a certain limit from said line are used for calculating the momentary masses m_n, which are then used for calculating the initial masses m_{0n}, and in that the calculated initial masses m_{0n} are used for estimating the actual initial mass m_0, for instance by taking the median or mean value of the calculated initial masses m_{0n}.

15. A method as claimed in claim 11 or 12, **characterized** in that the determination of a momentary mass m_1 is performed in another way, for example by analysing a blood sample or by equilibration of dialysate with blood and determining the actual concentration of the composition and by estimating or measuring the distribution volume of the composition.

16. A method as claimed in anyone of claims 3 - 15, **characterized** in that the distribution volume (V) of the composition fluid is estimated, for example by Watson's formula, and that the concentration of the composition in the fluid is determined by dividing the calculated mass with the volume.

17. A method as claimed in anyone of claims 3 - 15, **characterized** in that the concentration of the composition in the fluid is measured and that the distribution volume is determined by dividing the calculated mass and the concentration.

18. A method as claimed in anyone of claims 3 - 15, **characterized** in that the concentration of the composition in the fluid is measured by introducing a disturbance into the dialyser and measuring the resulting effect in the effluent dialysate and calculating the effective clearance of the dialyser from this resulting measurements, calculating the plasma water concentration of said substance by the formula:

$$c_{pw} = Q_d \times c_d / K_e$$

where

c_{pw}=plasma water concentration of urea at initiation of dialysis

Q_d = effluent dialysate flow rate

c_d = concentration of urea as extrapolated to the initiation

K_e = effective clearance of the dialyser for urea

and determining the distribution volume V of said substance by the formula:

$$V = m_0 / c_{pw}$$

where m_0 is determined according to any of the preceeding claims

19. A method as claimed in anyone of the preceding claims, **characterized** in that, after establishment of said approximation curve and determining a deviation of the concentration curve from the approximation curve, an alarm is emitted at deviation over or under a predetermined threshold level.

20. A method as claimed in any one of claims 3 to 9, **characterized** in that said parameter is the slope $[(K-UF)/V_0]$ of $\ln(c_d-c_k)$ as a function of $(V_0/UF)\ln(V/V_0)$ in the equation:

$$\ln(c_d-c_k) = \ln(c_0-c_k) + [(K-UF)/V_0]\cdot[(V_0/UF)\ln(V/V_0)] \quad (V)$$

where

c_d = dialysate concentration at time t

c_0 = dialysate concentration at time zero

c_k = $G/[Q_d\ (1 - UF/K)]$

G = solute generation

Q_d = dialysate flow

K = whole body clearance

V_0 = distribution volume before treatment (pre)

UF = ultrafiltration per time

21. A method as claimed in claim 20, **characterized** in that a momentary mass (m_1) is determined according to the equation:

$$m_1 = (Q_d \cdot c_{d1}) / (K/V)_1 \quad (VI)$$

where

$$(K/V)_1 = (K/V_0) / (1 - t_1 \cdot UF/V_0) \quad (VII)$$

with (K/V_0) determined according to equation (V) and UF/V_0 estimated, and in that the momentary relative efficiency $(K/V)_2$ at any time is determined according to equation:

$$(K/V)_2 = (Q_d \cdot c_{d2}) / m_2 \qquad \text{(VIII)}$$

where

$$m_2 = m_1 - (U_2 - U_1) + G\,(t_2 - t_1) \qquad \text{(IX)}$$

and

c_{d1} = concentration at time t_1

c_{d2} = concentration at time t_2

U_1 = accumulated mass to time t_1

U_2 = accumulated mass to time t_2.

22. An apparatus for calculating the mass of a composition in a fluid volume, comprising:

an exchanger for performing mass exchange between said volume and an exchange fluid flow,

a measuring apparatus for repeatedly measuring the concentration of said composition in the exchange fluid flow after said mass exchange for obtaining a concentration curve,

characterized by

first calculation means for fitting an approximation curve to at least a portion of said concentration curve, where the logarithm of said approximation curve is a substantially straight line,

second calculation means for determining a parameter of said approximation curve for use in calculating the mass of said composition in said volume.

23. An apparatus as claimed in claim 22, **characterized** in that said composition in a fluid volume is a solute in a liquid volume.

24. An apparatus as claimed in claim 23, **characterized** in that said exchanger is a dialyzer comprising a semi-permeable membrane, where said solute and exchange liquid passes on one side of said membrane and said exchange fluid is a dialysis

liquid passing on the other side of said membrane resulting in a dialysate liquid exiting the dialyzer.

25. An apparatus as claimed in claim 24, **characterized** by

a flow rate measuring means for measuring the flow rate Q_d of said dialysate liquid flow, and a third calculation means for calculating the accumulated mass of said solute in said dialysate liquid by integrating the product of said flow rate Q_d and said solute concentration c_d over time.

26. An apparatus as claimed in claim 24 or 25, **characterized** in that said dialysis liquid entering the dialyzer comprises a non-zero initial concentration of said composition, and that said measuring apparatus measures a concentration difference across the dialyzer.

27. An apparatus as claimed in claim 24, 25 or 26, **characterized** in that said first calculation means is adapted for subtracting a compensation term (G/Q_d) from said solute concentration (c_d) to obtain a compensated concentration, taking the logarithm of said compensated concentration and fitting a straight line to said logarithm of said compensated concentration, where said compensation term compensates for generation (G) of said solute.

28. An apparatus as claimed in any one of claims 22 to 27, **characterized** in that said parameter of said approximation curve is a slope of said substantially straight line.

29. An apparatus as claimed in any one of claims 22 to 28, **characterized** in that said first calculation means is adapted to exclude data obtained during an initiation period, of for example 60 minutes.

30. An apparatus as claimed in any one of claims 24 to 29, **characterized** in that said first calculation means is adapted to adjust the time scale, when the flow of dialysis liquid is interrupted for a first time period, by replacing said

first time period with a replacement time period which is shorter than said first time period.

31. An apparatus as claimed in any one of claims 24 to 30, **characterized** in that said second calculation means calculates said parameter as the slope (K/V) with respect to time (t) of equation:

$$\ln(c_d - G/Q_d) = \ln(c_0 - G/Q_d) - Kt/V \qquad (I)$$

where

c_d = dialysate concentration at time t

G = solute generation

Q_d = dialysate flow

c_0 = dialysate concentration at time zero

K/V = relative dialysis efficiency

t = time from time zero.

32. An apparatus as claimed in claim 31, **characterized** in that said second calculation means calculates a momentary mass (m_1) according to the equation:

$$m_1 = (Q_d \cdot c_{d1}) / (K/V)_1 \qquad (II)$$

where $(K/V)_1$ is determined according to equation (I), and in that the momentary relative efficiency $(K/V)_2$ at any time is determined according to equation:

$$(K/V)_2 = (Q_d \cdot c_{d2}) / m_2 \qquad (III)$$

where

$$m_2 = m_1 - (U_2 - U_1) + G\,(t_2 - t_1) \qquad (IV)$$

and

c_{d1} = concentration at time t_1

c_{d2} = concentration at time t_2

U_1 = accumulated mass to time t_1

U_2 = accumulated mass to time t_2.

33. An apparatus as claimed in claim 32, **characterized** in that said second calculation means is adapted to integrate the momentary relative efficiency (K/V) over time to give an estimate of the total dialysis dose Kt/V.

34. An apparatus as claimed in claim 22, **characterized** in that said second calculation means is adapted to fit said approximation curve by calculating a line which passes through the greatest number of points in the logarithm of the concentration curve, possibly compensated.

35. An apparatus as claimed in claim 34, **characterized** in that said second calculation means is adapted to use all values of concentration which are within a certain limit from said line for calculating the momentary masses m_n, which are then used for calculating the initial masses m_{0n}, and in that the calculated initial masses m_{0n} are used for estimating the actual initial mass m_0, for instance by taking the median or mean value of the initial masses m_{0n}..

36. An apparatus as claimed in claim 32 or 33, **characterized** by means for determining a momentary mass m_1 in another way, for example by analysing a blood sample or by equilibration of dialysate with blood and determining the actual concentration of the composition and by estimating or measuring the distribution volume of the composition.

37. An apparatus as claimed in anyone of claims 24 - 34, **characterized** by means for estimating the distribution volume (V) of the composition fluid, for example by Watson's formula, and that the concentration of the composition in the fluid is determined by dividing the calculated mass with the volume.

38. An apparatus as claimed in anyone of claims 24 - 36, **characterized** by means for measuring the concentration of the composition in the fluid and that the distribution volume is determined by dividing the calculated mass and the concentration.

39. An apparatus as claimed in anyone of claims 24 - 36, **characterized** by means for measuring the concentration of the composition in the fluid comprising means for introducing a disturbance into the dialyser and means for measuring the resulting effect in the effluent dialysate and means for

calculating the effective clearance of the dialyser from this resulting measurements, and means for calculating the plasma water concentration of said substance by the formula:

$$c_{pw} = Q_d \times c_d / K_e$$

where

c_{pw}=plasma water concentration of urea at initiation of dialysis

Q_d = effluent dialysate flow rate

c_d = concentration of urea as extrapolated to the initiation

K_e = effective clearance of the dialyser for urea

and means for determining the distribution volume V of said substance by the formula:

$$V = m_0 / c_{pw}$$

where m_0 is determined according to any of claims 24 - 38.

40. An apparatus as claimed in anyone of claims 22 - 39, **characterized** by means for determining a deviation of the concentration curve from the approximation curve, after establishment of said approximation curve, and emitting an alarm at deviation over or under a predetermined threshold level.

41. An apparatus as claimed in any one of claims 24 to 30, **characterized** in that said second calculation means calculates said parameter as the slope $[(K-UF)/V_0]$ of $\ln(c_d-c_k)$ as a function of $(V_0/UF)\ln(V/V_0)$ in the equation:

$$\ln(c_d-c_k) = \ln(c_0-c_k) + [(K-UF)/V_0]\cdot[(V_0/UF)\ln(V/V_0)] \quad (V)$$

where

c_d = dialysate concentration at time t

c_k = $G/[Q_d\ (1 - UF/K)]$

G = solute generation

Q_d = dialysate flow

c_0 = dialysate concentration at time zero

K/V = relative dialysis efficiency

UF = ultrafiltration per time

42. An apparatus as claimed in claim 41, **characterized** in that said second calculation means calculates a momentary mass (m_1) according to the equation:

$$m_1 = (Q_d \cdot c_{d1}) / (K/V)_1 \qquad \text{(VI)}$$

where

$$(K/V)_1 = (K/V_0) / (1 - t_1 \cdot UF/V_0) \qquad \text{(VII)}$$

with (K/V_0) determined according to equation (V) and UF/V_0 estimated, and in that the momentary relative efficiency $(K/V)_2$ at any time is determined according to equation:

$$(K/V)_2 = (Q_d \cdot c_{d2}) / m_2 \qquad \text{(VIII)}$$

where

$$m_2 = m_1 - (U_2 - U_1) + G\,(t_2 - t_1) \qquad \text{(IX)}$$

and

c_{d1} = concentration at time t_1

c_{d2} = concentration at time t_2

U_1 = accumulated mass to time t_1

U_2 = accumulated mass to time t_2.

Fig.1

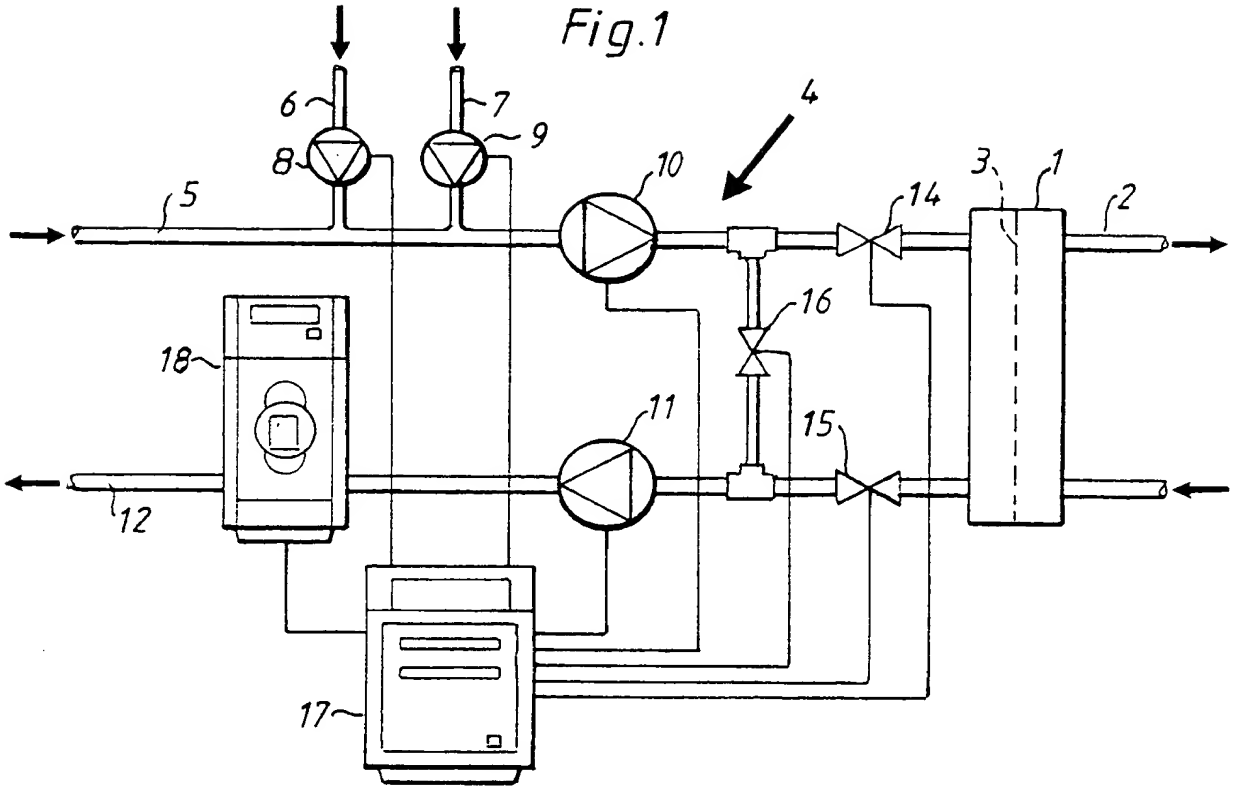


Fig.2

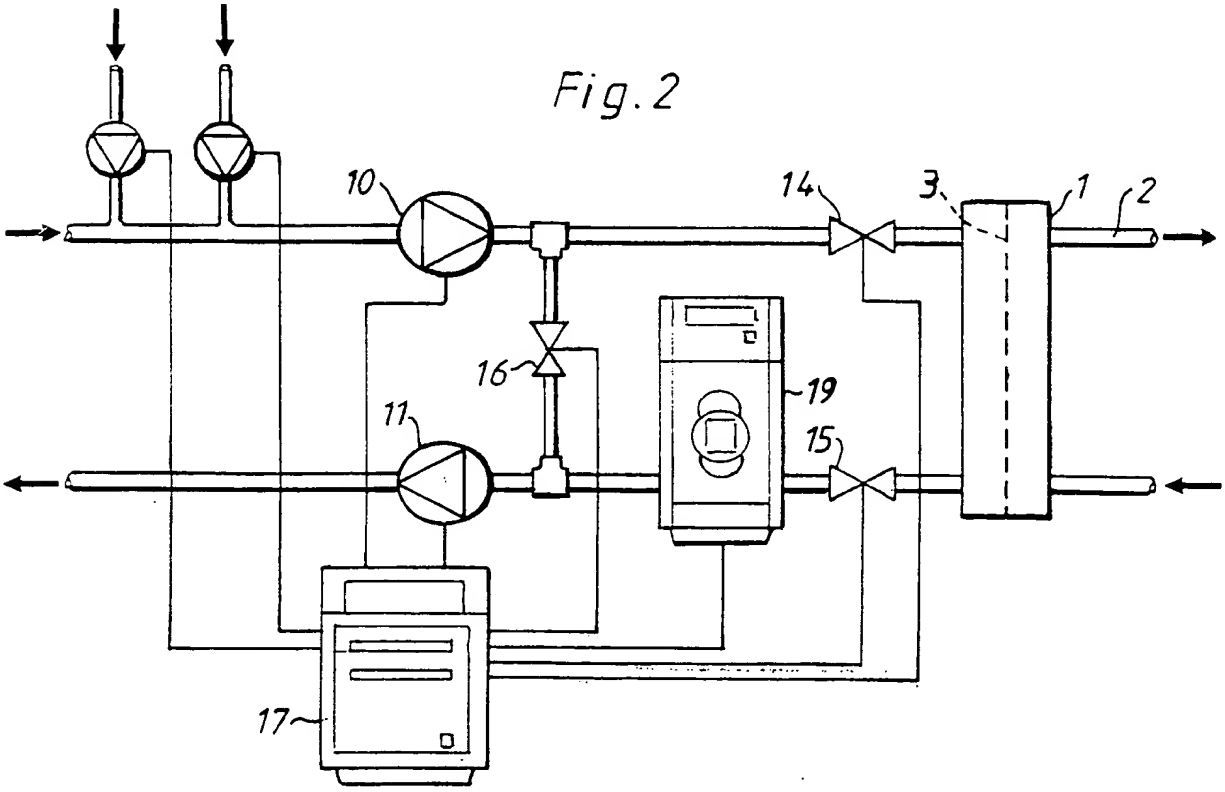


Fig.3

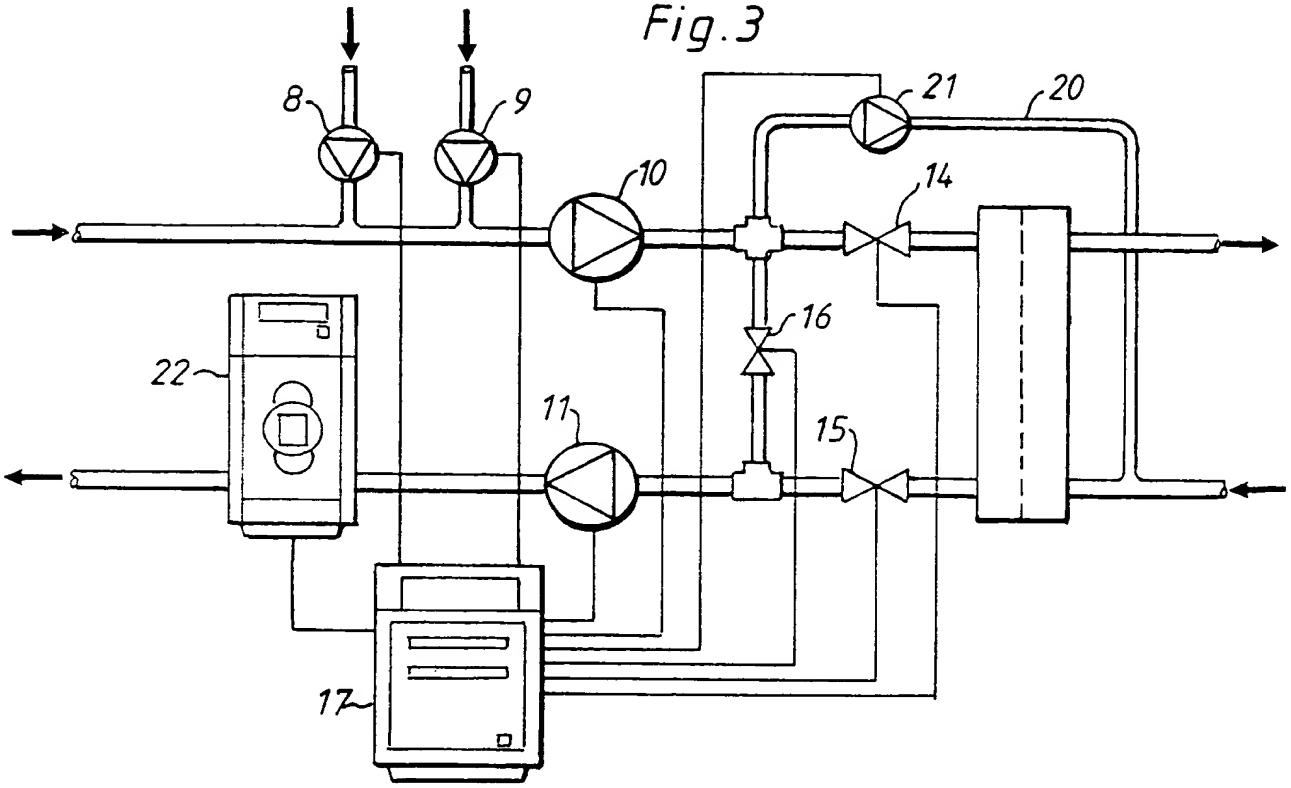


Fig.4

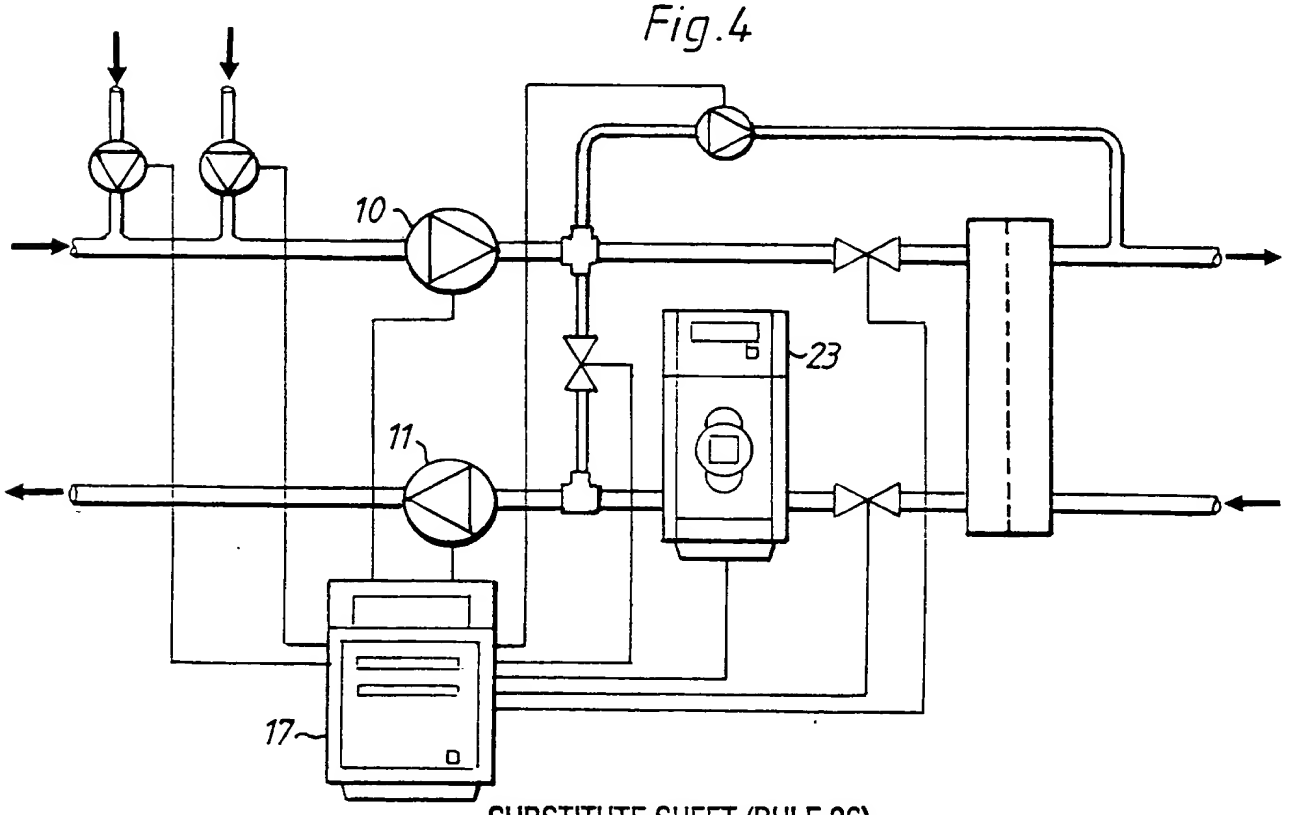


Fig.5

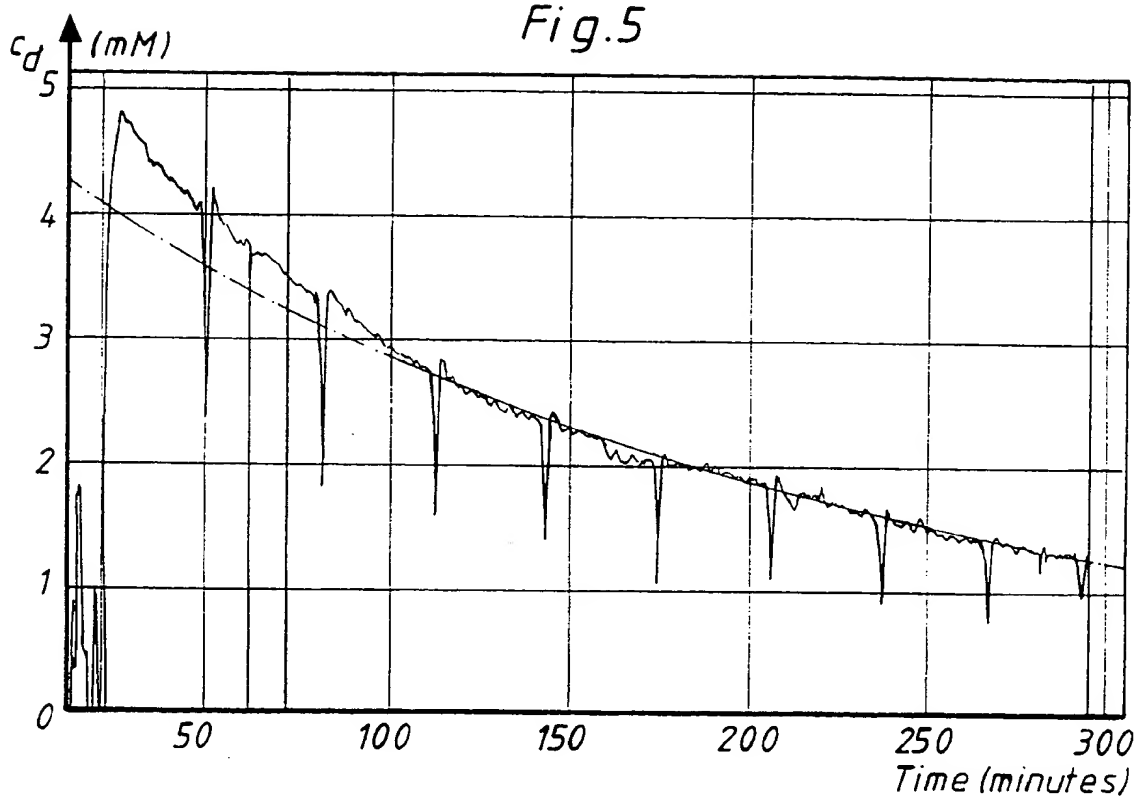


Fig.6

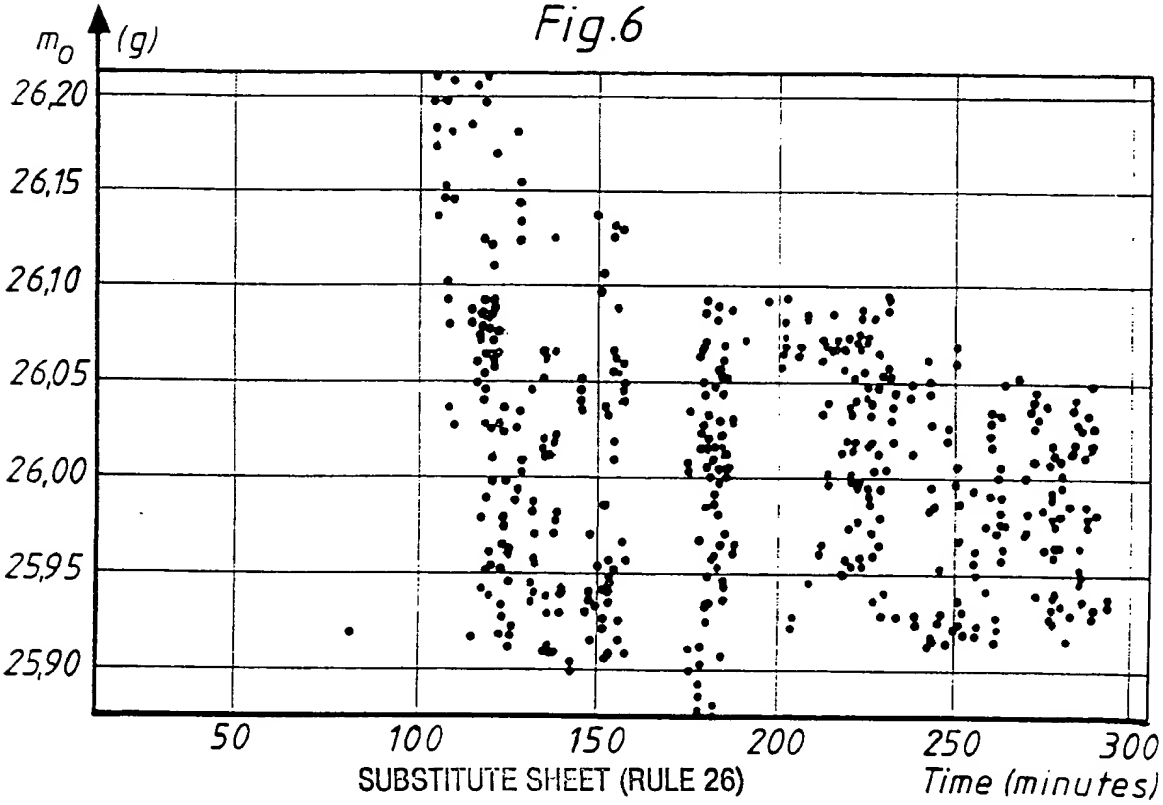


Fig.7

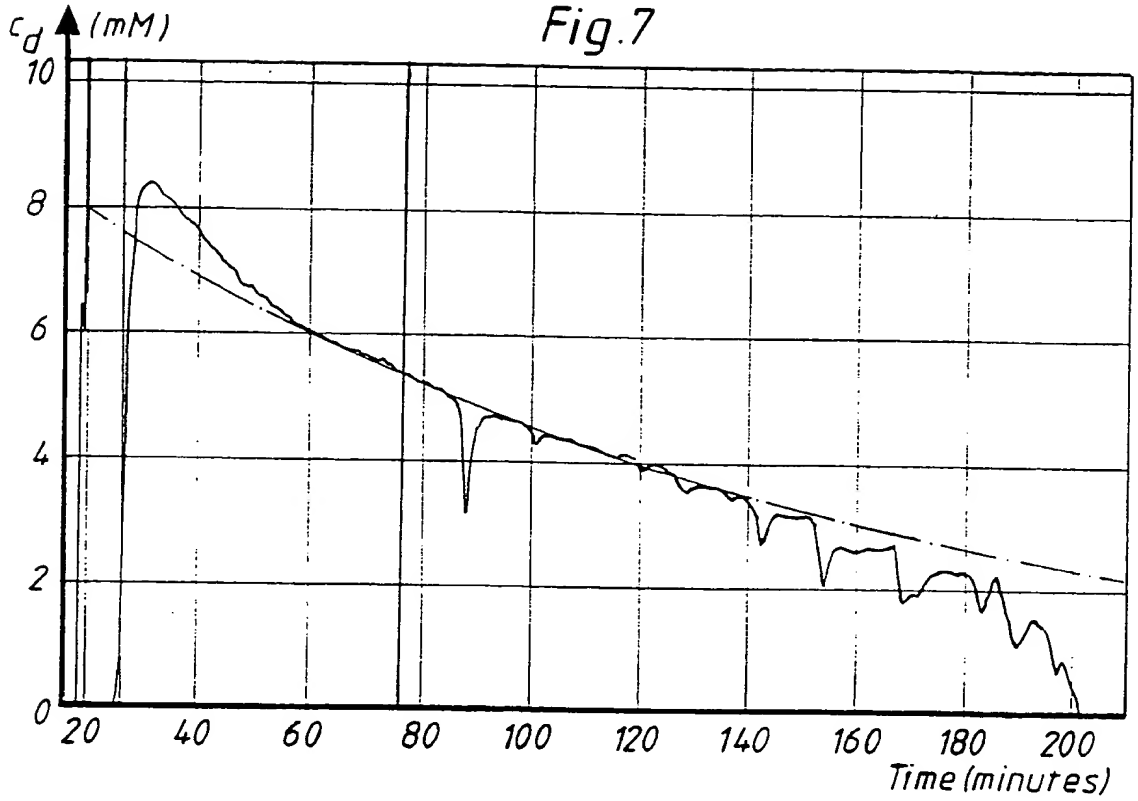


Fig.8

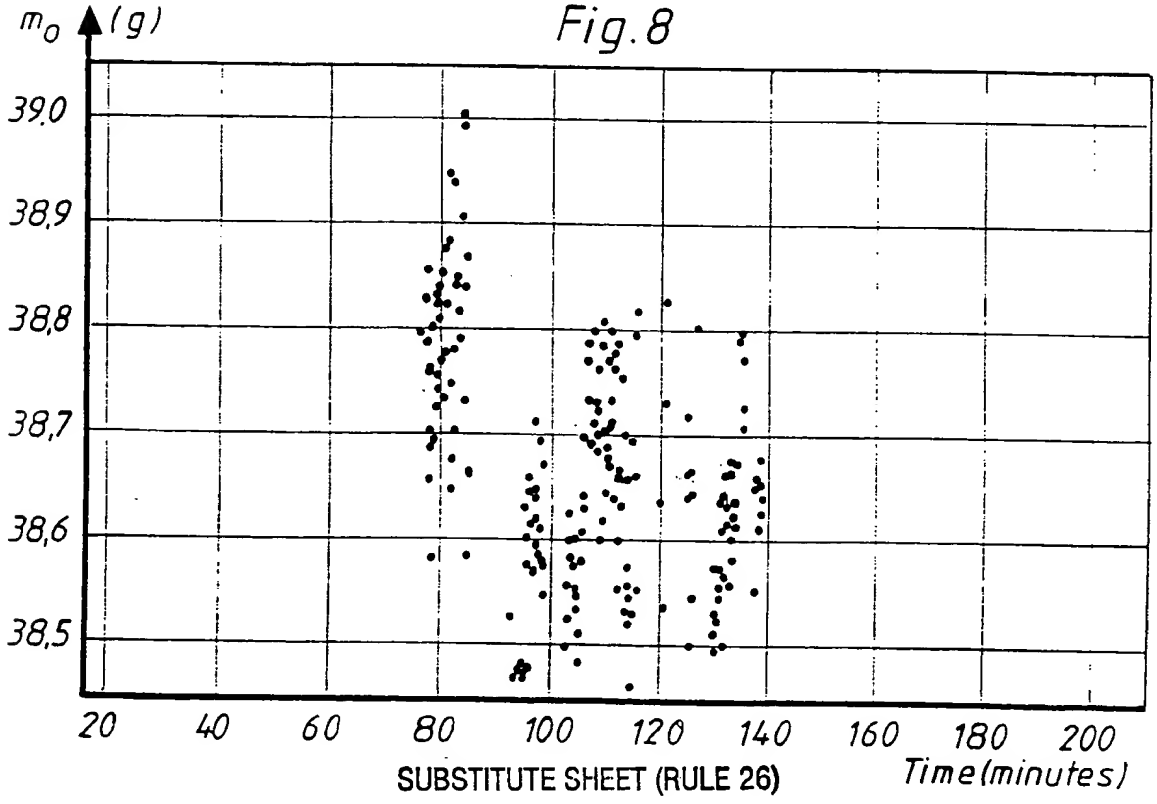


Fig.9

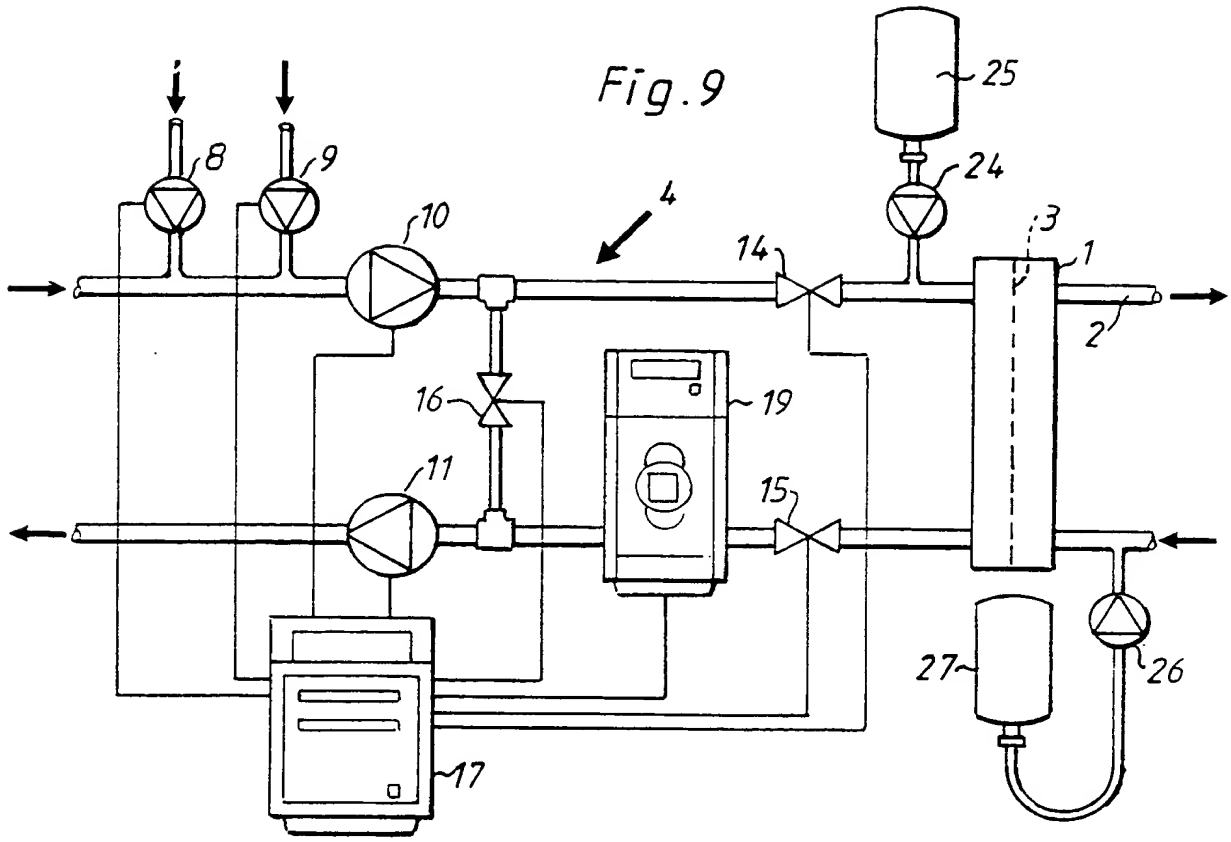
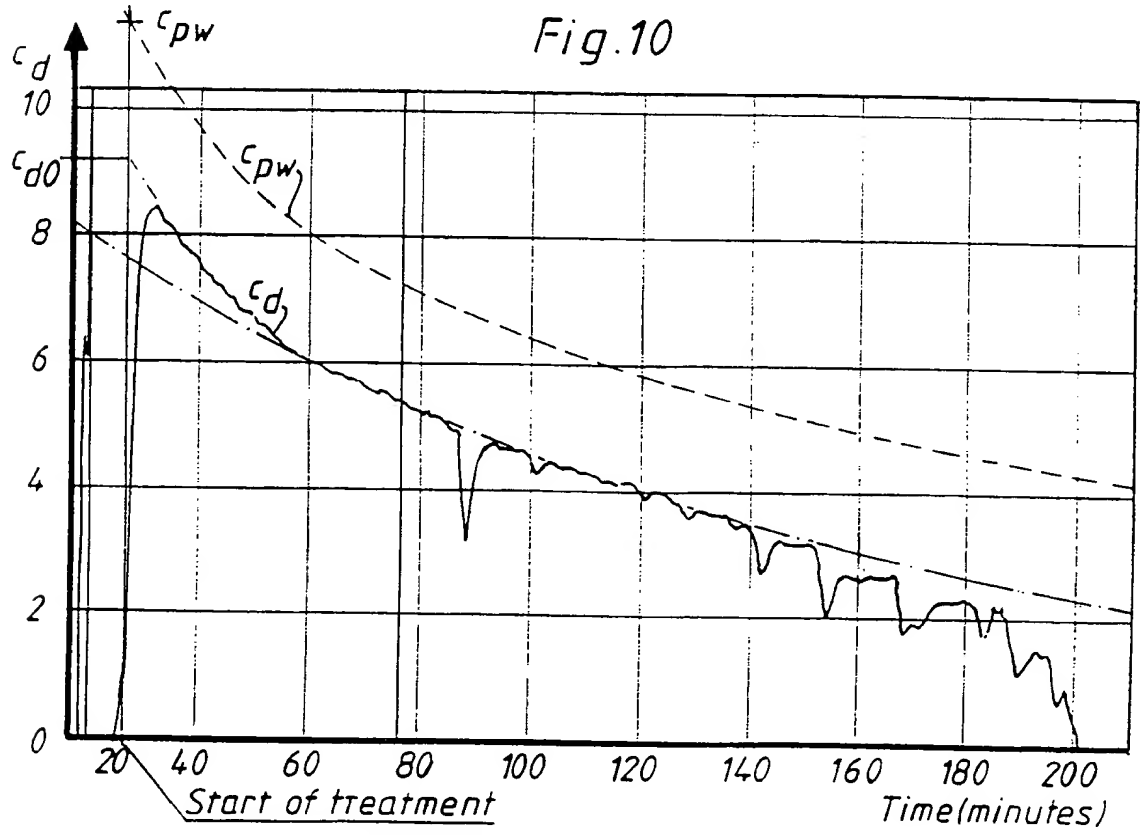


Fig.10



INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01048

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61M 1/14, G01N 33/487
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9408641 A1 (BAXTER INTERNATIONAL INC.), 28 April 1994 (28.04.94), page 17, line 3 - line 8; page 19, line 7 - page 22, line 6; page 26, line 10 - line 14	1-42
A	US 5598841 A (A.TANIJI ET AL), 4 February 1997 (04.02.97), column 8, line 25 - line 37	1-42
A	EP 0547025 A1 (GAMBRO AB), 16 June 1993 (16.06.93), column 4, line 38 - line 45	5,26
A	CA 2178430 A1 (COBE LABTRATORIES, INC.), 8 December 1996 (08.12.96), abstract	18,39

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 Sept 1998	11 -09- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Malin Keijser Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/01048

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No.
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